MASTER'S THESIS

Effects of Perfluorooctanesulfonic acid (PFOS) on Hypothalamic Metabolome and Testicular Function

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Persistent organic pollutants (POPs) are resistant to environmental degradation. In recent years, the adverse effects of these chemicals on general health have raised matters of serious public concern. Perfluorooctanesulfonic acid (PFOS) is a persistent organic pollutant and belongs to the family of poly- and per-fluoroalkyl substances (PFASs). It has been reported that PFOS can disturb the blood-testis barrier (BTB), adversely affecting the structure and function of Sertoli cells, Leydig cells and germ cells, thus disrupting the male reproductive system, reducing the testosterone level and the total sperm counts. Most of the studies examined the impact of PFOS on testicular function, while limited reports reviewed the effects of PFOS on the brain, specifically the hypothalamus, which is an integral part of the hypothalamic-pituitary-gonadal (HPG) axis. In chapter 2, we investigated the neurotoxic effects of PFOS. Immunostaining of the early response gene product c-Fos showed that PFOS activated lateral septum (LS), paraventricular nucleus of the thalamus (PVT), and the locus coeruleus (LC). No significant activation was found in the hypothalamus, such as paraventricular nucleus of the hypothalamus (PVN), medial preoptic area (mPOA), dorsomedial hypothalamus (DM), and ventromedial hypothalamus (VMH). Given the pivotal role of the hypothalamus in regulating reproductive function, we next investigated the metabolic profiling of the hypothalamus after 21 days of PFOS treatment. Principal compound analysis (PCA) showed that PFOS altered the hypothalamic metabolome. Several metabolites related to neurotransmitters and neuromodulators were altered, including N-docosahexaenoyl GABA, N-oleoyl GABA, N-palmitoyl GABA, DL-glutamate, pyroglutamic acid, D-pyroglutamic acid, L-tyrosine, and tryptophan. Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis showed that both 1 and 5 mg/kg PFOS altered amino acid metabolism (i.e., arginine, histidine, D-glutamine, D-glutamate, alanine, aspartate, glutamate and phenylalanine, tyrosine, and tryptophan). Metabolite set enrichment analysis (MSEA), based on the common differential metabolites, showed PFOS disturbed the metabolic pathways of the basic protein translation process, blood-brain barrier (BBB) integrity, and neurotransmitters and neuromodulators. Besides, the open field test (OFT) showed that PFOS exposed mice exhibited anxiety-like behavior as mice spent less time in the center and fewer entries to the center. In chapter 3, we evaluated the effects of 1 or 5 mg/kg PFOS on male fecundity after 21 days exposure. Results showed 5 mg/kg PFOS decreased serum luteinizing hormone (LH) levels. Furthermore, PFOS caused a decrease in caudal epididymal sperm activity. Sperm exhibited reduced curvilinear velocity (VCL), straight-line velocity (VSL), and average path velocity (VAP). Analysis of testicular transcriptome revealed that PFOS altered gene expression involved in spermatogenesis and steroidogenesis. Testicular transcriptome analysis showed that PFOS altered gene expression involved in spermatogenesis and steroidogenesis. Taken together, our results suggested that PFOS altered hypothalamic metabolome, reduced reproductive hormone levels, disrupted the process of spermatogenesis and steroidogenesis, and reduced sperm activity.